Remarks/Argument

Claims 1-4 are pending, and claims 5-16 have been canceled without prejudice to the filing of a divisional application. New claims 17-28 have been added. After entry of this amendment, Claims 1-4 and 17-28 will be pending. Applicants respectfully request reconsideration of claims 1-4, and favorable consideration of claims 17-28.

Support for amended claim 1 is found in claim 1 as originally filed. Claim 4 was amended to delete reference to the trademark Sandostatin® and replace it with the generic term "octreotide." One skilled in the art would know that "octreotide" is the generic name for "Sandostatin®"; see pg. 1 of "Drugs That Are Not Chemotherapy" from the Los Angeles Free-Net Health Center, downloaded from http://www.lafn.org/medical/po.bd.treatments.Sandost.html (enclosed). No new matter has been added by these amendments.

The new claims are directed to methods of producing antibodies in plants by using a viral vector. The new claims therefore fall within the elected invention, and can be prosecuted with claims 1-4.

New claims 17-23 are directed to methods in which plants are infected with at least two recombinant viral vectors. Each vector recited in new claims 17-23 comprises sequences which encode an antibody heavy or light chain, and viral sequences which complement the sequences from the other vector. Expression of viral sequences allows for systemic infection of the host plant with both vectors, and results in expression and assembly of the antibody sequences into full-length antibodies throughout the plant. Support for new claims 17-23 is found on pg. 4, lns. 13-17; pg. 7, lns. 9-12; pg. 17, lns. 5-21 and 26-30 of the present specification.

New claims 24-27 are directed to methods of producing antibodies in which plants are infected with a single recombinant viral vector. The vector comprises sequences which encode antibody heavy and light chains, and sequences which encode viral movement and capsid proteins from different viruses. Expression of the different movement and capsid proteins allows for systemic infection of the host plant with the vector, and results in expression and assembly of the antibody sequences into full-length antibodies throughout the plant. Support for new claims 24-27 is found on pg. 4, lns. 13-17; pg. 5, lns. 13-30; pg. 7, lns. 9-12; and pg. 17, lns. 5-21 of the present specification.

New claim 28 is directed to a method of producing antibodies in which plants are infected with three recombinant viral vectors. The first vector comprises sequences which encode viral movement and capsid proteins from different viruses. The second and third vectors comprise sequences which encode the same movement protein as the first vector and which encode either an antibody heavy or light chain. Expression of the movement and capsid proteins allows for systemic infection of the host plant with all three vectors, and results in expression and assembly of the antibody sequences into full-length antibodies throughout the plant. Support for new claim 28 is found on pg. 6, ln. 1 to pg. 7, ln. 3; pg. 7, lns. 9-12; and pg. 17, lns. 5-21 of the present specification.

Response to rejection under 35 U.S.C. 103(a)

The Examiner has maintained the rejection of claims 1-4 under 35 U.S.C. § 103(a) as obvious over US Pat. No. 5,316,931 to Donson et al. ("Donson '931) in view of Ma et al., 1994, Eur. J. Immunol. **24**:131-138 ("Ma"), U.S. Pat. No. 4,956,282 to Goodman et al. ("Goodman '282") and Donson et al., 1991, PNAS 88:7204-7208 ("Donson PNAS"). Applicants respectfully disagree.

To support a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Here, the cited references, either alone or in combination, do not suggest the claimed methods nor indicate that they could be practiced with any degree of success.

Claims 1-4 and new claims 17-23 and 28 recite methods of producing an antibody in a plant by infecting the plant with multiple recombinant viral vectors. The vectors carry some or all of the viral sequences needed for viral replication and for systemic infection of the host plant. The vectors also express the antibody heavy and light chain peptides, which are assembled in the plant into a full-length antibody.

Goodman '282 discloses that sequences encoding mammalian peptides can be inserted into the genome of plants, and that the resulting transgenic plant will express the mammalian peptide. Ma teaches that monoclonal antibodies can be expressed and assembled in transgenic plants in which the sequences encoding the foreign polypeptides have been inserted into the plant genome. Neither Ma nor Goodman '282 disclose or suggest that multiple recombinant viral vectors can be introduced into a plant by infection with the vectors, that the multiple vectors can cause systemic infection of the plant, or that expression and assembly of the antibody sequences can occur in the infected plant.

Donson '931 and Donson PNAS disclose the use of a single viral vector to introduce one or more foreign genes into a plants. The infected plants are systemically infected, and can express the foreign gene sequences. According to the Examiner, Donson '931 and Donson PNAS provide the motivation to use multiple viral vectors capable of systemic infection to express antibody heavy and light chains in plants. However, Donson '931 and Donson PNAS disclose only the use of a *single* recombinant viral vector, and do not suggest that multiple recombinant viral vectors can be used to express antibody sequences in plants.

Previously, the Examiner has argued that using multiple recombinant viruses is a simple extension of using a single vector, and is thus obvious to one of ordinary skill in the art. However, as stated before, one of ordinary skill in the art would not believe that multiple recombinant vectors could or should be used to deliver foreign genes to plant cells simply because single recombinant vectors have been used similarly in the past. One skilled in the art would also not assume that multiple viral vectors would necessarily cause systemic infection of a host plant.

Plants, like many other organisms, possess complex defenses against viral infection and replication. For example, plants infected with one viral strain can be protected from subsequent infection by a closely related viral strain. This process, called "cross protection," has been recognized since the 1920's (Waterhouse et al. (2001), Nature *411*, 834-842; copy enclosed). The mechanisms of cross protection are, however, still not well understood.

Cross protection in plant cells may be mediated by "plant disease resistance" (*R*) genes. The *R* genes encode receptors that recognize a specific pathogen-encoded ligand and initiate defense responses; *see* Dangl et al. (2001), Nature *411*, 826-833; copy enclosed. Other

mechanisms involved in cross protection may include virus-induced gene silencing (VIGS) or post-transcriptional gene silencing (PTGS). VIGS and PTGS are adaptive immune responses, meaning that a host plant can recognize viral nucleic acids and customize a sequence-specific response to clear viral infection; see Waterhouse et al., *supra*. Nucleic acid sequences which trigger VIGS or PTGS need not be viral sequences, as non-viral sequences present in viral vectors have triggered host plant defense systems. *See* Waterhouse et al., *supra*, pg. 835, which discusses a study performed in 1996 showing that plants sensitized to the β-glucuronidase ("GUS") gene were resistant to viral vectors containing GUS gene sequences.

Viral infection in plants can also induce the production of chemotactic factors, viral-binding lectins or "pathogenesis related" proteins that limit the spread of the virus throughout the plant; *see* Virology (2nd Edit.), Fraenkel-Conrat et al., Prentice-Hall, Inc. Englewood, NJ, 1988, pgs. 406-408 (enclosed). Finally, viral infection can have detrimental effects on plant growth even if the viral defenses discussed above are not triggered. For example, many viral infections cause "stunting"; that is, they cause the plant to remain abnormally small even if no other signs of viral infection are apparent. See Virology (2nd Edit.), Fraenkel-Conrat et al., *supra*, pg. 408.

Thus, one skilled in the art would have recognized, at the time the present application was filed, that plant cells exposed to one viral vector may be resistant to infection or replication of another viral vector. Multiple viral vectors, especially those which express the same or similar nucleic acid sequences, would not necessarily be expected to replicate or cause systemic infection in a host plant. Multiple viral infections would also be expected to detrimentally effect plant growth.

One skilled in the art would also have known, at the time the present application was filed, that introduction of any exogenous, self-replicating DNA (such as a recombinant viral vector) into a cell causes stress on that cell. Such stress results generally from maintaining or replicating the DNA in the cell, or from attempting to remove the exogenous DNA from the cell. Introduction of multiple self-replicating vectors into a cell would cause greater stress on a cell than introduction of a single vector. Absent any specific motivation to use multiple vectors, one skilled in the art would therefore consider methods which use a *single* viral vector to deliver foreign genes superior to methods using multiple viral vectors.

In contrast, the present claims recite the use of multiple viral vectors for causing the systemic infecting a host plant and the expression of antibody heavy and light chain sequences. As discussed above, this result was unexpected. Nevertheless, the claimed methods do produce systemic infection and the production of the full-length antibody in the host plant. *See* pg. 47, lns. 6-21 of the present specification.

Ma and Goodman '282 do not disclose the use of viral vectors to deliver foreign gene sequences into plants, not do these references discuss the desirability of delivering foreign genes with viral vectors. There is also no teaching or suggestion in Donson '931 or Donson PNAS that multiple viral vectors are preferable to single viral vectors for delivering foreign genes to plants. As discussed above, one skilled in the art would be skeptical that infection with multiple viral vectors would result in systemic infection of the host plant, with concomitant production of the foreign gene sequences, as is recited in claims 1-4, 17-23 and 28. The cited references would therefore not motivate one skilled in the art to produce the presently claimed methods, nor would these references provide a reasonable expectation that the claimed methods could be successfully practiced. Claims 1-4, 17-23 and 28 are therefore not obvious over the cited references.

Claims 24-27 recite methods of producing an antibody in a plant by infecting a host plant with a single viral vector. The claimed vector comprises sequences sequences encoding an antibody heavy and light chain, and sequences encoding a viral movement protein from one type of virus, and a viral capsid protein from another type of virus. These claims are not anticipated by Ma, Goodman '282, Donson '931 or Donson PNAS because none of these references disclose, either expressly or inherently, a single vector comprising sequences encoding a viral movement protein and a viral capsid protein from different viruses.

Claims 24-27 are also not rendered obvious by Ma, Goodman '282, Donson '931 or Donson PNAS because none of these references. The viral vector recited in claims 24-27 produces a systemic infection in a host plant. This systemic infection is facilitated by the production of a viral movement protein from one virus and the capsid protein of another virus from the viral vector. As stated in the present specification at pg. 17, ln. 26 to pg. 18, ln. 4:

> An unexpected aspect of the present invention is the discovery that the coat protein gene of a first class of virus (e.g., TMV) ciscomplements the long distance movement and encapsidation functions of a second class of virus (e.g., AMV) . . .

> Thus the complementation in the present invention can be applied rather broadly across various strains and even various genera including viruses and plants. The complementation functions thus achieved has the advantage in, among other things, reducing the selective pressure by the host plant, thereby facilitating the movement, assembly, or replication of the recombinant viral vectors and in extending the host range of the recombinant viruses.

Thus, the expression of viral movement and capsid proteins from different viruses allows the claimed viral vectors to avoid the plant viral defense systems discussed above, so that the vector can successfully replicate, infect the host plant systemically, and produce the full-length antibody. The viral movement and capsid proteins from different viruses can also be expressed from different viral vectors, as recited in claims 17-23 and 28, to achieve the same effect.

There is nothing in any of the cited references to suggest that expression of viral movement and capsid proteins from different viruses would confer a selective advantage on the vector(s) in the host plant. Thus, claims 17-28 are believed to be novel and unobvious over the references discussed above.

Conclusion

Based on the foregoing, all pending claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

HILARY KOPROWSKI *et al.*

BY: 

PAUL CARANGO
Registration No. 42,386
Drinker, Biddle & Reath, LLP
One Logan Square
18th and Cherry Streets
Philadelphia, PA 19103-6996
Phone: (215) 988-3312
Fax: (215) 988-2757
Attorney for Applicants